

In vivo* Toxicological Studies on Methanol Leaf Extract of *Lantana camara

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Abstract: Wide range of pharmaceutically active principles abound. However there is a dire need of knowledge about toxicological status of many of these medicinal plants. The study x-rayed the toxicological profile of *Lantana camara* with a view to elucidating its toxic nature. The acute toxicity test of the extracts on mice showed no toxicity up to 5000mg/kg body weight. Four groups of twelve rats were used. Sacrifices were carried out using three rats per group on the first, second, third and fourth weeks. This study showed significant decrease ($p < 0.05$) in alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP) activities in all the test groups in weeks 1 to 3, but significant increase ($p < 0.05$) was observed in all the test groups in week 4 compared to those of the control group. There were significant decreases ($p < 0.05$) in Na^+ and Cl^- concentrations in all the test groups in weeks 1 and 2. In week 3, there was no significant ($p > 0.05$) difference observed in the Na^+ and Cl^- concentration of Group 2 rats and no significant ($p > 0.05$) difference was observed in groups 3 and 4 rats. However, there was significant ($p < 0.05$) increases in Na^+ and Cl^- concentrations observed in all the test groups in week 4 compared to their control. There was significant ($p < 0.05$) increase in K^+ concentration in all test groups in week 1 while in week 2, there was no significant ($p > 0.05$) difference in all the test groups. Weeks 3 and 4 showed a significant ($p < 0.05$) decrease in K^+ concentration in all the test groups compared to those of their control group. Urea and creatinine concentrations decreased significantly ($p < 0.05$) in all the test groups in weeks 1, 2 and 3. However in week 4, there was significant ($p < 0.05$) increase observed in urea and creatinine concentrations compared to their control. These findings suggested a level of toxicity at chronic stage (beyond two weeks of administration of the extract) and therefore a serious caution in the use of this medicinal plant to avoid hepatic and renal biochemical distortion.

Key words: *Lantana camara* • ALT • AST • Electrolytes and Toxicological Studies

INTRODUCTION

The liver is a versatile organ which is involved in metabolism and independently involved in many other biochemical functions. Regenerating power of liver cells is tremendous [1]. The liver is endowed with various functions. It is the key organ and the principal site where the metabolism of carbohydrates, lipids and protein takes place. It is an organ where ammonia is converted to urea and principal organ where cholesterol is synthesized and catabolised to form bile acids and bile salts. They can detoxify drugs, hormones and convert them into less toxic substances for excretion [2, 3]. When the plasma membrane of hepatocyte is damaged, a variety of enzymes normally located in the cytosol are released into the blood stream. Their estimations in the serum are useful quantitative markers for the proper evaluation of liver

damage [4]. There is no glutamate dehydrogenase activity in normal serum but moderate elevation is found in most cases of acute hepatitis indicating cellular damage. Another demonstrable type of membrane damage involves injury to lysosomes which leads to the release of acid ribonuclease, acid phosphatases and other liver enzymes such as alanine amino-transaminase, aspartate amino-transaminase and alkaline phosphatase into the blood stream. These enzymes level are usually elevated in the blood during liver dysfunction to help distinguish and assess the degree of hepatocellular injury [5]. Alanine amino transferase (ALT), is primarily localized in the liver [6]. Alanine amino transferase is a cytosolic enzyme that catalyzes the transfer of the α -amino group from L-Alanine to α -ketoglutarate in the formation of hepatic injury and represents a marker of hepatocellular necrosis [7]. Aspartate aminotransferase (AST), is present

in a wide variety of tissues including heart, skeletal muscle, kidney, brain and liver. It is present both in the mitochondrial and cytosol of the hepatocytes and catalyze the transfer of the α -ketoglutarate resulting into formation of oxaloacetate and L-glutamate [8]. Serum alkaline phosphatase (ALP) is applied to a group of enzymes that catalyze hydrolysis of phosphate esters at an alkaline pH. The enzymes are present in various tissues such as liver, bone, intestine and placenta [9]. The most frequent cause of elevated total ALP activity in serum is disease of the liver or biliary tract. It is also elevated in various types of bone disease [10]. Bilirubin is a product of haemoglobin breakdown of red blood cells. The liver is responsible for its removal from the body via glucuronidation, catalysed by the enzyme glucuronyltransferase. Bilirubin is found in the body as total and conjugated bilirubin. An altered bilirubin level is indicative of liver damage when compared to plasma activities of serum enzymes in the liver [11]. When bilirubin in the blood exceeds 1mg/dl (17.1 μ mol/L) hyperbilirubinemia sets in. Hyperbilirubinemia may be due to the production of more bilirubin as a result from the failure of a damaged liver to conjugate and excrete bilirubin produced in normal amounts [12].

The primary roles of the kidney are to maintain an internal milieu that allows optimal cellular function and to remove toxins that are generated by metabolism or ingested with a diet. They keep the electrolytes (sodium and potassium being the most important) and water content of the body relatively constant. The most common waste products are urea and creatinine, but there are many other substances that need to be eliminated [13]. The kidneys act as very efficient filters for ridding the body of waste and toxic substances and returning vitamins, amino acids, glucose, hormones and other vital substances into the bloodstream. The kidneys receive a high blood flow and this is filtered by much specialised blood vessels. The fluid that is filtered is then adjusted by a complex series of urine-disposing tubes called tubules. In this way, the substances necessary for the good functioning of the body are retained and those that are not needed are excreted. This is vital to make the body function efficiently.

Lantana camara Linn, (Verbenaceae) is an ornamental weed with aromatic leaves. It is a low, erect vigorous shrub which can grow up to 2 - 4 meters in height. The leaves are bright green, rough, finely hairy and emit a pungent odour when crushed [14]. The ripe fruit is benign and heavily consumed by birds and

frequently eaten by humans in some countries. Many lantana varieties are poisonous to livestock. The toxins in lantana include the triterpene acids {lantadeneA (rehmannic acid)}, lantadene B and their reduced forms [15]. *Lantana camara* has been used in many parts of the world to treat a wide variety of disorders [16]. In central and North America, the leaves are made into a poultice to treat sores, chicken pox and measles. Fevers, colds, rheumatism, asthma and high blood pressure were treated with preparations from the plant [17]. The leaves are also used to treat cuts, rheumatism, ulcers and intestinal worms. Beside these, the leaves of the plant are boiled for tea and the decoction is a remedy against cough and it is used as a lotion for wounds. Pounded leaves are applied to cuts, ulcers and swellings [18]. The methanol extract of *Lantana camara* leaves have shown healing potential against gastric ulcer in humans [19]. Leaf extracts of *Lantana* exhibit antioxidant, antihypertensive, antimicrobial, fungicidal, insecticidal and nematocidal properties [20- 23]. *Lantana camara* oil is sometimes used for the treatment of skin itches, as an antiseptic for wounds and externally for leprosy and scabies [24].

Lantana camara is one among the most toxic plants known so far, possibly within top ten. Reports of *Lantana camara* toxicity have been reported from Australia, India, New Zealand, South Africa and America. However, the toxicity occurs only on the consumption of high amount of the plant material [25]. It has been reported to make animals ill after ingestion. Its foliage contains the toxic pentacyclitriterpenoids called lantadenes. Major lantadenes are A, B, C and D and reduced lantadene A and reduced lantadene B. Lantadene A and Lantadene B cause hepatotoxicity and photosensitivity in grazing animals such as sheep, goats and bovines and horses [26]. *Lantana camara* extract is a powerful febrifuge as the leaves and some other parts of lantana are poisonous, care must be taken when it is used medicinally. The *Lantana camara* root extracts are the most toxic part although it has anticancer activity [27]. Pharmacological investigations indicated that extracts of leaves of *Lantana camara* exhibited strong antioxidant activities.

Plant Material: The leaves of *Lantana Camara* were used for this study. They were collected from Amokwe village Nsukka Enugu State, Nigeria and were identified by Mr. Alfred Ozioko of the Bioresources Development and Conservation Programme (BDCP) Research Centre Nsukka, Enugu State.

Animals: Forty eight (48) adult albino rats were used for the studies and eighteen (18) albino mice were used for the acute toxicity (LD_{50}) study. All the animals used were purchased from the Animal house of the Faculty of Biological Sciences, University of Nigeria, Nsukka. The rats were fed with standard grower's mash rat pellets (Grand Cereals LTD, Enugu) and water. The guide for the care and use of Laboratory animals procedures were followed in this study.

Equipment/ Chemicals: The equipment used were obtained from the Department of Biochemistry and other scientific shops in Nsukka. The chemicals and reagents used were of analytical grade

Preparation of Plant Material: The fresh leaves of *Lantana camara* were collected from Amokwe village, washed with clean water to remove dirt and drained. They were dried under shade for several days and then pulverised into powder.

Extraction of Plant Material: A quantity (500g) of the powdered leaves of *Lantana camara* was macerated in one litre of methanol for 24 h. The solution was filtered with Whatman no.1 filter paper and the filtrate was concentrated to a semi-solid residue using rotary evaporator.

Acute Toxicity Test: The method of Lorke [28] was used for the acute toxicity test. Eighteen albino (18) mice were utilized in this study. The test involved two stages. In stage one; the animals were grouped into three groups of three rats each. They were administered 10, 100 and 1000mg/Kg body weight of the extract respectively and in the second stage, 1600, 2900 and 5000mg/Kg body weight of the extract were administered to the animals. The administration of the extract was done orally. The animals were then observed over a 24 hour period for nervousness, dullness, in-coordination or death.

Experimental Design: Forty eight (48) Wistar albino rats weighing 105-200g were used for the study. They were acclimatized for seven (7) days with free access to feed and water. After acclimatization, they were evenly distributed into four groups of twelve rats each. The extract was given orally for a period of four weeks. The rats, three (3) from each group were sacrificed at a weekly interval from each group. The animals were grouped and dosed as follows:

Group 1: Control (received normal saline)

Group 2: Normal rats +100mg/kg body weight of the extract

Group 3: Normal rats + 200mg/kg body weight of the extract

Group 4: Normal rats + 500mg/kg body weight of the extract

Alanine Amino Transferase (ALT) and Aspartate Amino Transferase (AST): Alanine amino-transaminase (ALT) and aspartate amino-transferase (AST) were determined using the method of Reitman and Frankel [29] as outlined in Randox test kit (USA).

Alkaline Phosphatase (ALP): Alkaline phosphatase activity was assayed using the method of Klein *et al.* [30].

Determination of Potassium Ion Concentration: The concentration of potassium ion (K^+) was determined using the method of Henry *et al.* [31].

Determination of Sodium Ion Concentration: The concentration of Sodium ion (Na^+) was determined using the method of Maruna [32].

Determination of Chloride Ion Concentration: The concentration of chloride ion (Cl^-) was determined using the method of Skeggs and Hochstrasser [33].

Determination of Serum Urea Concentration: The concentration of serum urea was determined using the method of Chaney and Marbach [34].

Determination of Serum Creatinine Concentration: The concentration of serum creatinine was determined using the method of Bartels *et al.* [35].

Statistical Analysis: Data were reported as means \pm SEM, where appropriate. One way analysis of variance (ANOVA) was used and Duncan multiple test range was used to compare the group means obtained after each treatment with control measurement. $P < 0.05$ was considered significant. Statistical Product and Service Solution (SPSS) version 20 were used.

RESULTS

The acute toxicity test of the leaves of *Lantana camara* showed no death up to 5000mg/kg body weight. Hence it is relatively safe at 5000mg/kg body weight.

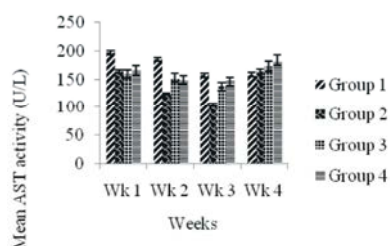


Fig. 1: Effect of Methanol Extract of *Lantana camara* Leaves on AST Activity of Albino Rats

Group 1: Control (Normal Saline 5 ml/kg body weight)
 Group 2: Normal rats +100mg/kg body weight
 Group 3: Normal rats + 200mg/kg body weight
 Group 4: Normal rats + 500mg/kg body weight

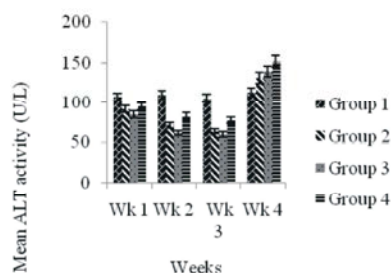


Fig. 2: Effect of Methanol Extract of *Lantana camara* Leaves on ALT Activity of Albino Rats

Group 1: Control (Normal Saline 5 ml/kg body weight)
 Group 2: Normal rats +100mg/kg body weight
 Group 3: Normal rats + 200mg/kg body weight
 Group 4: Normal rats + 500mg/kg body weight

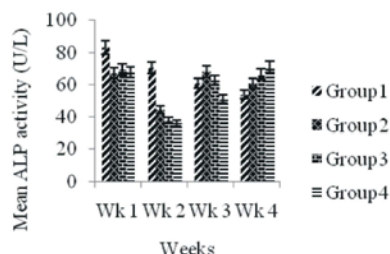


Fig. 3: Effect of Methanol Extract of *Lantana camara* Leaves on ALP Activity of Albino Rats

Group 1: Control (Normal Saline 5 ml/kg body weight)
 Group 2: Normal rats +100mg/kg body weight
 Group 3: Normal rats + 200mg/kg body weight
 Group 4: Normal rats + 500mg/kg body weight

Effect of Methanol Extract of *Lantana camara* Leaves on Aspartate Transaminase (AST) Activity: The result of AST indicated a significant ($P < 0.05$) decrease in serum

AST in the entire test groups (2, 3 and 4) up to week three. In week four, group 2 showed non significant ($P > 0.05$) increase, while there were significant ($P < 0.05$) decreases in groups 3 and 4 when compared to the control group.

Effect of Methanol Extract Of *Lantana camara* Leaves on Alanine Transaminase (ALT) of Rats: Figure 2 showed that there were a significant decreases ($p < 0.05$) in serum ALT activity in all the test groups (2, 3 and 4) up to week three. In week four, there were significant increases ($p < 0.05$) in all the test groups (2, 3 and 4) when compared to the control group (1).

Effect of Methanol Extract of *Lantana camara* Leaves on Alkaline Phosphatase (ALP) of Rats: As shown in Fig. 3, there were significant ($p < 0.05$) decreases in serum ALP in all the test groups (2, 3 and 4) in weeks one and two. In week three, significant ($p < 0.05$) increase was observed in groups 2 and 3 except group 4 that showed significant ($p < 0.05$) decrease. In week four, all the test groups (2, 3 and 4) showed significant ($p < 0.05$) increases when compared to the control group 1.

Effect of Methanol Extract of *Lantana camara* leaves on Direct Bilirubin of Rats: The result shown in Fig. 4, indicated that there was significant ($p < 0.05$) decrease in direct bilirubin level in all the groups except group 2 in week one. In week two, all the groups showed significant ($p < 0.05$) decrease, while there was significant ($p < 0.05$) decrease in group 2 and no significant ($p > 0.05$) increase in group 3 and 4 in week three. In week four, there was significant ($p < 0.05$) increase in all the test groups when compared to control group 1.

Effect of Methanol Extract of *Lantana camara* leaves on Total Bilirubin of Rats: Fig. 5, showed that there was significant ($p < 0.05$) decrease in total bilirubin in all the test groups in weeks one and two. In week three, there was a significant ($p < 0.05$) increase in all the test groups except group 2 that showed a significant ($p < 0.05$) decrease. In week four, there were significant ($p < 0.05$) increases in all the test groups when compared to the control group 1.

Effect of Methanol Leaves Extract of *Lantana camara* on Serum Urea Concentration: As shown in Fig. 6, there were significant ($p < 0.05$) decrease observed in serum urea level in all the test groups (2, 3 and 4) at weeks one, two and three. In week four, all the groups showed a significant ($p < 0.05$) increase except group 2 that do not show a significant ($p > 0.05$) increase.

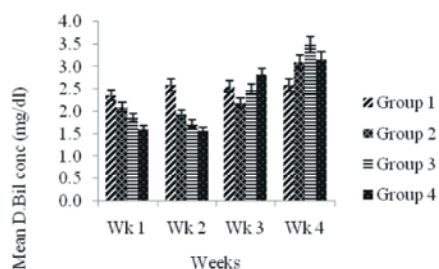


Fig. 4: Effect of Methanol Extract of *Lantana camara* Leaves on Direct Bilirubin Concentration of Albino Rats

Group 1: Control (Normal Saline 5 ml/kg body weight)
 Group 2: Normal rats +100mg/kg body weight
 Group 3: Normal rats + 200mg/kg body weight
 Group 4: Normal rats + 500mg/kg body weight

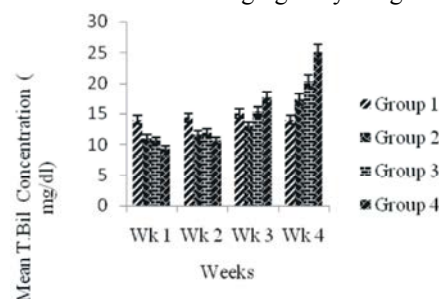


Fig. 5: Effect of Methanol Extract of *Lantana camara* Leaves on Total Bilirubin Concentration of Albino Rats

Group 1: Control (Normal Saline 5 ml/kg body weight)
 Group 2: Normal rats +100mg/kg body weight
 Group 3: Normal rats + 200mg/kg body weight
 Group 4: Normal rats + 500mg/kg body weight

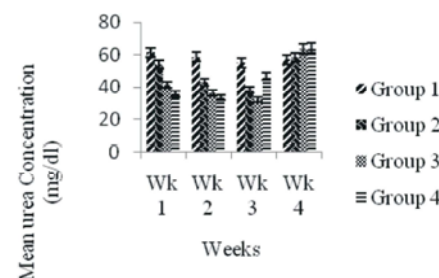


Fig. 6: Effect of methanol extract of *Lantana camara* leaves on urea concentration of albino rats

Group 1: Control (Normal Saline 5 ml/kg body weight)
 Group 2: Normal rats +100mg/kg body weight
 Group 3: Normal rats + 200mg/kg body weight
 Group 4: Normal rats + 500mg/kg body weight

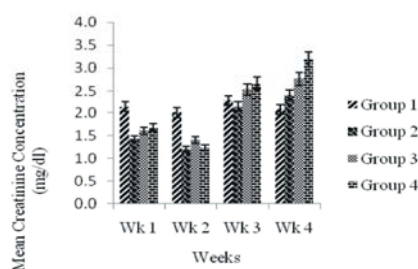


Fig. 7: Effect of Methanol Extract of *Lantana camara* Leaves on Creatinine Concentration of Albino Rats

Group 1: Control (Normal Saline 5 ml/kg body weight)
 Group 2: Normal rats +100mg/kg body weight
 Group 3: Normal rats + 200mg/kg body weight
 Group 4: Normal rats + 500mg/kg body weight

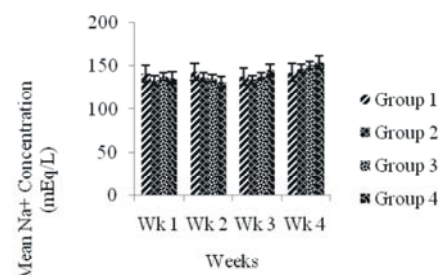


Fig. 8: Effect of Methanol Extract of *Lantana camara* Leaves on Sodium Ion (Na⁺) Concentration of Albino Rats

Group 1: Control (Normal Saline 5 ml/kg body weight)
 Group 2: Normal rats +100mg/kg body weight
 Group 3: Normal rats + 200mg/kg body weight
 Group 4: Normal rats + 500mg/kg body weight

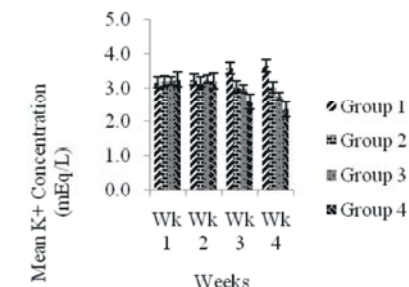


Fig. 9: Effect of the Methanol Extract of *Lantana camara* Leaves on Potassium Ion (K⁺) Concentration of Albino Rats

Group 1: Control (Normal Saline 5 ml/kg body weight)
 Group 2: Normal rats +100mg/kg body weight
 Group 3: Normal rats + 200mg/kg body weight
 Group 4: Normal rats + 500mg/kg body weight

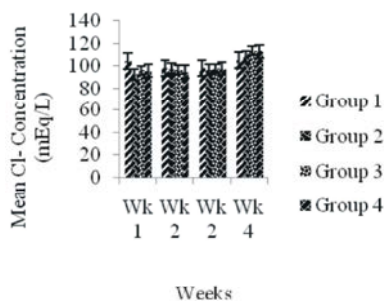


Fig. 10: Effect of the Methanol Extract of *Lantana camara* Leaves on Chloride Ion (Cl⁻) Concentration of Albino Rats

Group 1: Control (Normal Saline 5 ml/kg body weight)

Group 2: Normal rats +100mg/kg body weight

Group 3: Normal rats + 200mg/kg body weight

Group 4: Normal rats + 500mg/kg body weight

Effect of Methanol Extract of *Lantana camara* Leaves on Serum Creatinine Concentration: There was a significant ($p < 0.05$) decrease in serum creatinine concentration in the test groups at weeks one and two. In week three, group 2 did not show any significant ($p > 0.05$) decrease in creatinine level while groups 3 and 4 showed a significant ($p < 0.05$) increase in creatinine level. In week four, there was a significant increase in all the groups when compared to that of the control group 1, as shown in Fig. 7.

Effect of Methanol Extract of *Lantana camara* Leaves on Sodium Ion (Na⁺) Concentration in Rats: In Fig. 7, the result showed a significant decrease ($p < 0.05$) in serum sodium ion concentration in the test groups (2, 3 and 4) in weeks one and two, while in week three, there was no significant ($p > 0.05$) decrease in group 2, no significant increase in group 3. While there was a significant increase in group 4. In week four, there was a significant ($p < 0.05$) increase in all the test groups compared to the control group 1.

Effect of Methanol Extract of *Lantana camara* Leaves on Serum Potassium Ion (K⁺) Concentration: Fig. 9, showed a significant ($p < 0.05$) increase in potassium ion concentration of rats in all the test groups in week one. In week two, there were no significant ($p > 0.05$) decreases observed in K⁺ concentration of rats in all the test groups. In weeks three and four, there were significant ($p < 0.05$) decreases in all the compared to the control rats in group 1.

Effect of Methanol Extract of *Lantana camara* Leaves on Chloride Ion (Cl⁻) Concentration of Rats: Significant ($p < 0.05$) decrease were observed in serum chloride ion concentration of rats in all test groups (2, 3 and 4) in week one. However there was no significant ($p > 0.05$) change in the concentration of chloride ion in the rats of all the test groups in weeks two and three. In week four, there were significant ($p < 0.05$) increase in all the test groups compared to those of the rats in group 1 which served as the control as shown in Fig. 10.

DISCUSSION

The toxicological studies on the extract suggested that *Lantana camara* leaves possess some level of toxicity on hepatocytes and kidneys on prolonged administration. The acute toxicity test (LD₅₀) result signifies a relative safety within this 24 hour duration. The observations seen in ALT, AST and ALP activities could indicate that the extract may tend to prevent liver damage by maintaining the integrity of the plasma membrane at acute phase (within two weeks of administration); thereby suppressing the leakage of this enzyme through the membrane, exhibiting hepatoprotective activity which might arise from the hepatoprotective effect of some of the other plant constituents such as oleanolic acid as reported by Misra *et al.* [4]. The significant increase ($p < 0.05$) in all the test groups at the chronic phase (beyond two weeks of administration) however, could suggest necrosis of the hepatocytes or hepatocellular damage due to accumulation of toxic compounds such as triterpenoid (lantadene A, B and C) present in the plant. Triterpenoid was found to have toxic effect on rats fed with the extract as suggested by the findings of Mello *et al.* [3] who reported toxicological effect of *Lantana camara* on liver, general reproductive performance and teratology in rats on prolong treatment. Several studies have reported similar elevation in the activities of serum AST, ALT and ALP during prolonged administration of *Lantana camara* the extract [19, 25].

Liver is involved in the metabolism of bilirubin [14, 26]. The extract caused significant decrease ($p < 0.05$) in the direct and total bilirubin concentration of rats in all the test groups in weeks one and two, suggesting that the extract probably protects the liver by enhancing bilirubin uptake and conjugation by the liver and subsequent secretion into the bile ducts. The significant increase ($p \leq 0.05$) in direct and total bilirubin concentration in all the groups in weeks three and four could be due to the

inhibition of binding, conjugation and excretory capacity of hepatocytes due to prolonged administration of the extract.

The renal function test of the rats showed a significant decrease ($p < 0.05$) in serum urea and creatinine concentration of rats in all test groups in weeks one and two but increased in week four. The decrease in concentration may be an indication that the plant extract does not pose any toxic effect on the kidney at this and could subsequently have no effect on the erythropoietin production at this phase while the elevated urea and creatinine level signified a possible impaired kidney function. Impairment of the kidney leads to rise in creatinine level in blood [12, 23]. There was no significant increase ($p > 0.05$) in serum sodium ion concentration in all the test groups in weeks one and two, thereby suggesting that there is no kidney damage at this phase. There was significant increase ($p < 0.05$) in serum potassium ion concentration in all the test groups in weeks one and two, followed by significant decrease ($p < 0.05$) in week four, this could be an indication of an underlying kidney dysfunction or damage to the kidney at the chronic phase. Chloride concentration showed significant increase ($p < 0.05$) in all the test groups in week four. There could be an injury on the kidney tissues at this phase. This suggested that the extract's toxicity increased both with time and dosage.

CONCLUSION

These findings suggested a level of toxicity at chronic stage (beyond two weeks of administration of the extract) and therefore a serious caution in the use of this medicinal plant to avoid hepatic and renal biochemical distortions. However its medicinal potency and reduced toxicity at acute phase (within two weeks of administration) is a welcome development.

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